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DOI: https://doi.org/10.1055/s-0031-1299744

Synthesis of Cyclopentapyridine and Thienopyridine Derivatives as Potential Calcium Channel Modulators

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Abstract

In this study, novel condensed 1,4-dihydropyridines bearing cyclopentanone (1-21) or tetrahydrothiophene-1,1-dioxide ring (22-42) with various ester substituents were synthesized via modified Hantzsch reaction and their calcium channel modulator activities were investigated on isolated rat ileum and rat thoracic aorta. The introduction of cyclopentanone ring as fused to the 1,4-dihydropyridine nucleus and methyl, ethyl and allyl moieties to the ester group led to more active calcium modulators.

Key words: 1,4-Dihydropyridine, Thienopyridine, Cyclopentapyridine, Calcium channel modulator

1. Introduction

Calcium ions play a critical role in various biological functions such as muscle contraction, release of neurotransmitters and regulation of neuronal excitability [1]. Calcium entry into the cytosol is mediated by different types of calcium channel with distinct physiological roles [2]. L-type channels are confined to cell bodies and regulate contractions in muscle cells. Calcium channel antagonists block Ca^{2+} influx through L-type calcium channels reversibly [3]. 1,4-Dihydropyridines (DHP), of which nifedipine is the prototype, are one of the known class of calcium antagonists, which are frequently used for the treatment of cardiovascular diseases like angina, hypertension and supraventricular tachycardia [4-6].

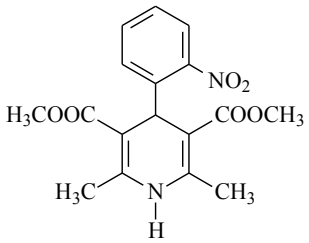


Figure 1: Nifedipine

Since the introduction of DHPs into clinical use, many DHP analogs have been synthesized in order to elucidate the structure-activity relationships and to enhance calcium-modulating effects [7]. It was reported that active derivatives could be obtained by introducing the DHP structure into condensed ring systems such as hexahydroquinolines, indenopyridines, acridines and furoquinolines [8-11]. C-3 and C-5 substituents modulate activity and tissue selectivity and different substituents in these positions alter the activity [12]. Studies of fused 1,4-DHPs, in which one of the ester groups is immobilized, indicate that at least one ester group must be *cis* to the double bond of DHP for hydrogen bonding to the receptor [13]. As the substituent at C-4 position, phenyl is preferred because of animal toxicity observed with heteroaromatic rings [14]. Phenyl groups which possess one or more electron-withdrawing substituents at *ortho*- or *meta*-position are preferable to other groups such as alkyls or phenyl groups having a substituent at *para*-position [15, 16].

The aim of this work is to evaluate the influence of the cyclopentane or tetrahydrothiophene rings, fused to DHP ring and various ester groups in combination with two halogens attached to the phenyl ring in the 1,4-DHP nucleus. The compounds were synthesized and tested as racemates. The calcium modulator activities of the compounds were assayed on isolated rat ileum and rat thoracic aorta. Although compound **37** was synthesized before by Dodd and co-

workers [17], since there is no data about its calcium channel modulatory activity on ileum and aorta, it was also synthesized in this study.

2. Material and Methods

2.1. Chemistry

2.1.1. General Methods

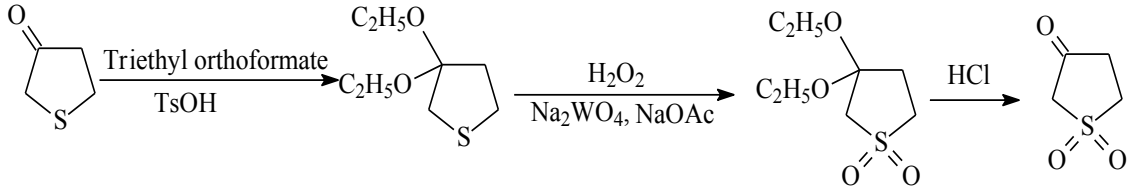
All chemicals used in this study were purchased from Aldrich and Fluka. Melting points were determined on Thomas Hoover Capillary Melting Point Apparatus and are uncorrected. Infrared spectra were recorded on Perkin Elmer FT-IR Spectrum BX. ^{1}H-NMR, ^{13}C-NMR DEPT and COSY spectra were obtained in dimethyl sulphoxide (DMSO) solutions on Varian Mercury 400, 400 MHz High Performance Digital FT-NMR Spectrometer. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane. The X-ray crystallographic analysis was carried on Nonius Kappa CCD area-detector diffractometer. Mass spectra were obtained on Agilent 5973 Network Mass Selective Detector by electron ionization. Elemental analyses were performed on Leco CHNS-932 Elemental Analyzer. Purification by column chromatography was carried on Merck silica gel 60 (0.040-0.063 mm).

2.1.2. Synthesis

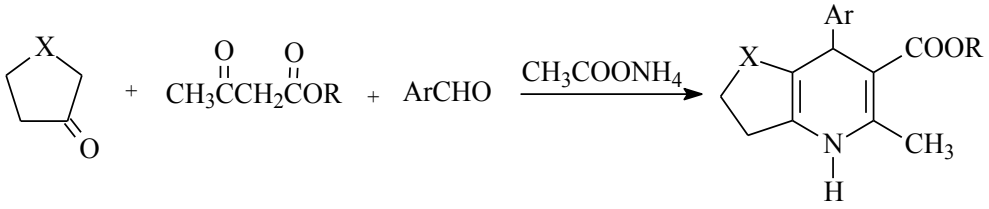
The compounds were synthesized according to Scheme 1 and 2.

The synthesis of tetrahydrothiophene-3-one-1,1-dioxide is reported in Scheme 1. 0,1 mol tetrahydrothiophen-3-one, 0,1 mol triethyl orthoformate, 0,13 mmol p-toluensulfonic acid an 2 mL ethanol was stirred for 20 hours. The mixture was treated with 4 mmol anhydrous sodium acetate, 0,00085 mmol sodium tungstate dehydrate and 28 mL water. 28 mL 35 % solution of hydrogen peroxide in water was added dropwise while keeping the reaction cooled to 30 $^{\circ}$C. After stirring over night at room temperature, the resulting product was filtered and washed with water to achieve 3,3-diethoxytetrahydrothiephene-1,1-dione. The product was stirred in a mixture of HCl and water at 60 °C for 2 hours. The mixture was treated with dichloromethane. The dichloromethane layer was isolated and dried with $MgSO_4$, filtered and concentrated. The residue was crystallized from ethanol to provide tetrahydrothiophene-3-one-1,1-dioxide [18].

The compounds **1-42** were prepared (Scheme 2) by heating 1,3-cyclopentanedione or tetrahydrothiophene-3-one-1,1-dioxide, aromatic aldehyde, appropriate acetoacetate compound and ammonium acetate in methanol, according to Hantzsch reaction.



Scheme 1.



Scheme 2.

X: CO (Compound **1-21**), SO_2 (Compound **22-42**)

Ar: 2,3-difluorophenyl, 2-fluoro-3-chlorophenyl, 2,3-dichlorophenyl

R: -CH_3, -C_2H_5, -$CH_2CH_2OCH_3$, -CH_2-CH=CH_2, -$CH_2CH(CH_3)_2$, -$C(CH_3)_3$, -$CH_2C_6H_5$

Alkyl 2-methyl-4-(2,3-disubstitutedphenyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (Compound 1-21):

1,3-Cyclopentanedione (0,001 mol), 2,3-disubstituted benzaldehyde (0,001 mol), alkyl acetoacetate (0,001 mol) and ammonium acetate (0,005 mol) were refluxed for 8 h. in 15 mL methanol. After the reaction was completed, either the reaction mixture was poored into ice-water, the obtained precipitate was filtered and crystallized from appropriate solvents or the solvent (methanol) was removed via rotary evaporator and the crude product was then purified by column chromatography using silica gel as the solid phase and a 7:3 mixture of ethyl acetate: methanol as mobile phase.

Alkyl 5-methyl-7-(2,3-disubstitutedphenyl)-2,3,4,7-tetrahydrothieno[3,2-b]pyridine-6-carboxylate-1,1-dioxide (Compound 22-42):

Tetrahydrothiophene-3-on-1,1-dioxide (0,001 mol), 2,3-disubstituted benzaldehyde (0,001 mol), alkyl acetoacetate (0,001 mol) and ammonium acetate (0,005 mol) were refluxed for 8 h. in 15 mL methanol. The precipitate, which was obtained after cooling the reaction mixture, was crystallized from methanol.

2.2. Pharmacology

The calcium antagonistic activities of the compounds were determined by the tests performed on isolated rat ileum and rat thoracic aorta. All procedures involving animals and their care were conducted in conformity with international laws and policies.

All data are expressed as mean ± standard error. Statistical comparison between groups was performed using general linear models and p values, less than 0,005, were considered to be statistically significant.

2.2.1. Studies on isolated rat ileum

Albino rats of either sex weighing 150-200 g were used in pharmacological studies. The animals were supplied from the Laboratory Animal Production Center in the Department of Pharmacology, School of Medicine, Osmangazi University, Eskişehir, Turkey. The animals used in the test were fasted overnight. After the animals were sacrificed by cervical dislocation, the ileum (10-15 cm terminal portion) was immediately removed, discarding the 5-8 cm segment proximal to the ileocaecal junction. Segments 1.5-2 cm long were mounted vertically in a 10 ml organ bath containing Tyrode solution of the following composition (mmol/L): NaCl: 136.87, KCl: 2.68, $CaCl_2$: 1.80, $MgSO_4$: 0.81, NaH_2PO_4: 4.16, $NaHCO_3$: 11.9, glucose: 5.55. The bath contents were maintained at 37 $^{\circ}$C and aerated by 95 % O_2 and 5 % CO_2. A tension of 2 g was applied and isometric recording was done by using isometric transducer (FDT_{10}-A) May TDA95 Transducer Data Acquisition System (May, Commat, Ankara, Turkey). The preparations were allowed to equilibrate for 60 min with regular washes every 15 min. In order to check calcium antagonistic effects, contractions were induced with barium chloride (4.10^{-3} mol/L, bath concentration). After washing out, this process was repeated until the amplitude of the contraction became constant. Investigations of the substances were performed using the single-dose technique. Barium chloride contractions were induced after addition of the test substances dissolved in DMSO at 10^{-5} M concentration and 5 min exposure time. Only one compound was tested in each preparation [19].

2.2.2. Studies on rat thoracic artery

Rat thoracic artery preparations were also obtained from the same animals, which were used for isolated rat ileum experiments. Rings (3 mm) were suspended in organ baths of 10 mL capacity which contained Tyrode solution. The bath contents were maintained a 37 $^{\circ}$C and aerated by 95 % O_2 and 5 % CO_2. A tension of 2 g was applied. The preparations were

allowed to equilibrate for 60 min with regular washes every 15 min. In order to check calcium antagonistic effects, contractions were induced with 67 mmol/L potassium chloride. After washing out, this process was repeated until the amplitude of the contractions became constant. Investigations of the substances were performed using single-dose technique. Potassium chloride contractions were induced after addition of the test substance and 10 min exposure time. During the administration of the individual substances, the preparation was washed until the initial situation had been re-established and the potassium chloride contractions were induced. The isometric contractions were recorded by an isometric transducer (FDT10-A) May TDA95 Transducer Data Acquisition System [20].

3. Results

3.1. Chemistry

Methyl 2-methyl-4-(2,3-difluorophenyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (Compound 1): Purified via column chromatography. Yield: 45%. mp: 223 ºC. IR (ν, cm^{-1}): 3288 (N-H), 1699 (C=O, ester), 1638 (C=O, ketone). ^{1}H-NMR (δ, DMSO-d_6): 2.17-2.56 (4H; m; H-6, H-7), 2.27 (3H; s; 2-CH_3), 3.40 (3H; s; $COOCH_3$), 4.91 (1H; s; H-4), 6.89-7.15 (3H; m; Ar-H), 9.82 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 19.2, 24.2, 31.3, 33.8, 51.2, 102.8, 115.1, 124.7, 125.8, 136.7, 147.2, 148.6, 150.9, 151.1, 164.7, 167.3, 201.0. MS (m/z): 319 $[M]^+$. Anal. Calcd. for $C_{17}H_{15}F_2NO_3$: C, 63.95; H, 4.73; N, 4.39. Found: C, 63.49; H, 4.61; N, 4.43.

Ethyl 2-methyl-4-(2,3-difluorophenyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (Compound 2): Purified via column chromatography. Yield: 60%. mp: 211 ºC'dir. IR (ν, cm^{-1}): 3275 (N-H), 1698 (C=O, ester), 1634 (C=O, ketone). ^{1}H-NMR (δ, DMSO-d_6): 0.99 (3H; t; $COOCH_2C\underline{H}_3$), 2.19-2.57 (4H; m; H-6, H-7), 2.31 (3H; s; 2-CH_3), 3.90 (2H; q; $COO\underline{CH}_2CH_3$), 4.95 (1H; s; H-4), 6.92-7.16 (3H; m; Ar-H), 9.83 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 13.6, 18.6, 23.7, 30.7, 33.3, 59.0, 102.4, 114.4, 114.9, 124.2, 125.3, 136.5, 136.6, 146.7, 148.0, 164.2, 166.2, 200.5. MS (m/z): 333 $[M]^+$. Anal. Calcd. for $C_{18}H_{17}F_2NO_3$: C, 64.86; H, 5.14; N, 4.20. Found: C, 64.67; H, 4.55; N, 4.38.

2-Methoxyethyl 2-methyl-4-(2,3-difluorophenyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (Compound 3): Purified via column chromatography. Yield: 46%. mp: 156 ºC. IR (ν, cm^{-1}): 3268 (N-H), 1680 (C=O, ester), 1642 (C=O, ketone).

^{1}H-NMR (δ, DMSO-d_6): 2.19-2.57 (4H; m; H-6, H-7), 2.31 (3H, s, 2-CH_3), 3.15 (3H; s; OCH3), 3.31-3.38 (2H; m; C$\underline{H}_2$OCH$_3$), 3.90-4.02 (2H; m; C$\underline{H}_2$CH$_2$OCH$_3$), 4.95 (H; s; 4-H), 6.92-7.15 (3H; m; Ar-H), 9.85 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 18.7, 23.7, 30.7, 33.3, 57.8, 62.3, 69.6, 102.1, 114.4, 115.0, 124.1, 125.3, 136.3, 145.7, 148.1, 150.5, 164.1, 166.2, 200.5. MS (m/z): 363 $[M]^+$. Anal. Calcd. for $C_{19}H_{19}F_2NO_4$: C, 62.81; H, 5.27; N, 3.85. Found: C, 62.16; H, 4.98; N, 3.98.

Allyl 2-methyl-4-(2,3-difluorophenyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (Compound 4): Crystallized from benzene/petroleum ether. Yield: 41%. mp: 183 ºC. IR (ν, cm^{-1}): 3282 (N-H), 1686 (C=O, ester), 1640 (C=O, ketone). ^{1}H-NMR (δ, DMSO-d_6): 2.14-2.57 (4H; m; H-6, H-7), 2.23 (3H; s; 2-CH_3), 4.37 (H; dd; C$\underline{H}_{2A}$-CH=CH$_2$), 4.43 (H; dd; C$\underline{H}_{2B}$-CH=CH$_2$), 4.97 (H; dd; CH$_2$CH=C$\underline{H}_{2A}$), 4.98 (H; s; 4-H), 5.04 (H; dd; CH$_2$CH=C$\underline{H}_{2B}$) 5.66-5.75 (H; m; C$\underline{H}$=CH$_2$), 6.93-7.15 (3H; m; Ar-H), 9.86 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 18.8, 23.7, 30.7, 33.3, 63.7, 102.0, 114.7, 115.0, 116.8, 124.2, 125.2, 132.7, 136.3, 136.4, 145.4, 147.3, 164.1, 165.9, 200.5. MS (m/z): 345 $[M]^+$. Anal. Calcd. for $C_{19}H_{17}F_2NO_3$: C, 66.08; H, 4.96; N, 4.06. Found: C, 65.11; H, 4.60; N, 4.09.

Isobutyl 2-methyl-4-(2,3-difluorophenyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (Compound 5): Crystallized from ethyl acetate/n-hexane**.** Yield: 52%. mp: 168 ºC. IR (ν, cm^{-1}): 3314 (N-H), 1690 (C=O, ester), 1646 (C=O, ketone). ^{1}H-NMR (δ, DMSO-d_6): 0.67 (3H, d, COOCH$_2$CHC$\underline{H}_3$), 0.73 (3H, d, COO CH$_2$CHC$\underline{H}_3$), 1.67-1.75 (H; m; C$\underline{H}$(CH$_3$)$_2$), 2.15-2.55 (4H; m; H-6, H-7), 2.33 (3H, s, 2-CH_3), 3.63 (H; dd; C$\underline{H}_A$CH(CH$_3$)$_2$), 3.71 (H; dd; C$\underline{H}_B$CH(CH$_3$)$_2$), 4.97 (H; s; 4-H), 6.93-7.17 (3H; m; Ar-H), 9.79 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 18.6, 18.8, 19.1, 23.6, 27.1, 30.6, 33.3, 69.3, 102.1, 114.4, 124.2, 125.1, 136.4, 145.3, 147.2, 148.2, 150.5, 164.0, 166.3, 200.4. MS (m/z): 360 $[M-1]^+$. Anal. Calcd. for $C_{20}H_{21}F_2NO_3$: C, 66.47; H, 5.86; N, 3.88. Found: C, 66.24; H, 5.86; N, 3.94.

Tert-butyl 2-methyl-4-(2,3-difluorophenyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (Compound 6): Crystallized from ethyl acetate/n-hexane. Yield: 48%. mp: 196 ºC. IR (ν, cm^{-1}): 3302 (N-H), 1696 (C=O, ester), 1632 (C=O, ketone). ^{1}H-NMR (δ, DMSO-d_6): 1.16 (9H; s; COOC(C$\underline{H}_3$)$_3$), 2.12-2.52 (4H; m; H-6, H-7), 2.24 (3H; s; 2-CH_3), 4.88 (H; s; 4-H), 6.89-7.34 (3H; m; Ar-H), 9.67 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 18.9, 23.9, 24.0, 24.1, 28.0, 31.5, 33.7, 79.4, 104.3, 115.0, 124.6, 125.8, 136.9,

145.9, 146.1, 148.6, 150.9, 164.5, 166.2, 200.9. MS (m/z): 360 $[M-1]^+$. Anal. Calcd. for $C_{20}H_{21}F_2NO_3$: C, 66.47; H, 5.86; N, 3.88. Found: C, 66.40; H, 5.80; N, 3.85.

Benzyl 2-methyl-4-(2,3-difluorophenyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (Compound 7): Crystallized from ethyl acetate/n-hexane. Yield: 54%. mp: 202 ºC. IR (ν, cm^{-1}): 3260 (N-H), 1695 (C=O, ester), 1630 (C=O, ketone).^{1}H-NMR (δ, DMSO-d_6): 2.19-2.57 (4H; m; H-6, H-7), 2.33 (3H; s; 2-CH_3), 4.93, 5.02 (1H, AB system, J_{AB}=12.8 Hz, COOC$\underline{H}_2C_6H_5$), 4.99 (1H; s; H-4), 6.90-7.27 (8H; m; Ar-H), 9.77 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 18.8, 23.7, 30.7, 33.3, 64.7, 101.8, 114.5, 115.0, 124.1, 125.2, 127.4, 127.6, 128.1, 136.2, 145.4, 145.6, 147.5, 147.9, 148.1, 150.5, 164.0, 166.1, 200.5. MS (m/z): 395 $[M]^+$. Anal. Calcd. for $C_{23}H_{19}F_2NO_3$: C, 69.87; H, 4.84; N, 3.54. Found: C, 69.25; H, 4.77; N, 3.61.

Methyl 2-methyl-4-(2-fluoro-3-chlorophenyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (Compound 8): Purified via column chromatography. Yield: 52%. mp: 245 ºC. IR (ν, cm^{-1}): 3268 (N-H), 1709 (C=O, ester), 1634 (C=O, ketone). ^{1}H-NMR (δ, DMSO-d_6): 2.20-2.59 (4H; m; H-6, H-7), 2.30 (3H; s; 2-CH_3), 3.44 (3H; s; $COOCH_3$), 4.93 (1H; s; H-4), 7.06-7.34 (3H; m; Ar-H), 9.85 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 18.7, 23.7, 31.5, 33.3, 50.6, 102.3, 114.8, 119.2, 124.9, 128.1, 129.2, 135.6, 146.8, 155.5, 164.3, 166.8, 200.5. MS (m/z): 334 $[M-1]^+$. Anal. Calcd. for $C_{17}H_{15}ClFNO_3$: C, 60.81; H, 4.50; N, 4.17. Found: C, 60.13; H, 4.66; N, 4.29.

Ethyl 2-methyl-4-(2-fluoro-3-chlorophenyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (Compound 9): Purified via column chromatography. Yield: 64%. mp: 239 ºC. IR (ν, cm^{-1}): 3272 (N-H), 1698 (C=O, ester), 1632 (C=O, ketone). ^{1}H-NMR (δ, DMSO-d_6): 0.98 (3H; t; $COOCH_2C\underline{H}_3$), 2.20-2.58 (4H; m; H-6, H-7), 2.30 (3H; s; 2-CH_3), 3.87 (2H; q; $COOC\underline{H}_2CH_3$), 4.94 (1H; s; H-4), 7.06-7.34 (3H; m; Ar-H), 9.84 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 13.6, 18.6, 23.7, 31.2, 33.3, 59.0, 102.4, 114.9, 119.1, 124.9, 129.2, 135.9, 146.7, 152.9, 155.4, 164.2, 166.2, 200.5. MS (m/z): 349 $[M]^+$. Anal. Calcd. for $C_{18}H_{17}ClFNO_3$: C, 61.81; H, 4.90; N, 4.00. Found: C, 61.37; H, 5.10; N, 4.11.

2-Methoxyethyl 2-methyl-4-(2-fluoro-3-chlorophenyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (Compound 10): Purified via column chromatography. Yield: 51%. mp: 158 ºC. IR (ν, cm^{-1}): 3319 (N-H), 1696 (C=O, ester), 1637

(C=O, ketone). ^{1}H-NMR (δ, DMSO-d_6): 2.12-2.57 (4H; m; H-6, H-7), 2.31 (3H, s, 2-CH_3), 3.15 (3H; s; OCH3), 3.31-3.42 (2H; m; $C\underline{H}_2OCH_3$), 3.91-4.02 (2H; m; $C\underline{H}_2CH_2OCH_3$), 4.95 (H; s; 4-H), 6.92-7.17 (3H; m; Ar-H), 9.85 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 19.2, 24.2, 31.9, 36.4, 58.4, 64.8, 70.1, 102.6, 115.4, 125.3, 128.5, 129.7, 131.8, 136.1, 147.7, 153.6, 156.1,166.7, 200.5. MS (m/z): 379 $[M]^+$. Anal. Calcd. for $C_{19}H_{19}ClFNO_4$: C, 60.08; H, 5.04; N, 3.69. Found: C, 59.99; H, 4.99; N, 3.73.

Allyl 2-methyl-4-(2-fluoro-3-chlorophenyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (Compound 11): Purified via column chromatography. Yield: 49%. mp: 194 ºC. IR (ν, cm^{-1}): 3265 (N-H), 1740 (C=O, ester), 1712 (C=O, ketone). ^{1}H-NMR (δ, DMSO-d_6): 2.15-2.58 (4H; m; H-6, H-7), 2.32 (3H; s; 2-CH_3), 4.36 (H; dd; $C\underline{H}_{2A}$-CH=CH_2), 4.25 (H; dd; $C\underline{H}_{2B}$-CH=CH_2), 4.96 (H; s; 4-H), 4.99 (H; dd; $CH_2CH=C\underline{H}_{2A}$), 5.05 (H; dd; $CH_2CH=C\underline{H}_{2B}$), 5.65-5.76 (H; m; $C\underline{H}=CH_2$), 7.06-7.33 (3H; m; Ar-H), 9.85 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 18.8, 23.7, 31.3, 33.3, 63.7, 102.1, 117.0, 119.2, 124.9, 128.0, 129.1, 132.6, 135.7, 147.3, 153.0, 155.4, 164.2, 165.9, 200.5. MS (m/z): 361 $[M]^+$. Anal. Calcd. for $C_{19}H_{17}ClFNO_3$: C, 63.08; H, 4.74; N, 3.87. Found: C, 62.97; H, 4.89; N, 3.90.

Isobutyl 2-methyl-4-(2-fluoro-3-chlorophenyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (Compound 12): Purified via column chromatography. Yield: 56%. mp: 163 ºC. IR (ν, cm^{-1}): 3254 (N-H), 1697 (C=O, ester), 1628 (C=O, ketone). ^{1}H-NMR (δ, DMSO-d_6): 0.65 (3H; d; $COOCH_2CHC\underline{H}_3$), 0.72 (3H; d; COO $CH_2CHC\underline{H}_3$), 1.66-1.74 (H; m; $C\underline{H}(CH_3)_2$), 2.14-2.57 (4H; m; H-6, H-7), 2.33 (3H; s; 2-CH_3), 3.60 (H; dd; $C\underline{H}_{2A}CH(CH_3)_2$), 3.71 (H; dd; $C\underline{H}_{2B}CH(CH_3)_2$), 4.95 (H; s; 4-H), 7.07-7.33 (3H; m; Ar-H), 9.86 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 18.5, 18.6, 18.8, 23.7, 27.1, 31.1, 33.3, 69.4, 102.1, 115.0, 119.3, 125.0, 129.0, 135.9, 147.3, 152.8, 155.3, 164.1, 166.3, 200.4. MS (m/z): 377 $[M]^+$. Anal. Calcd. for $C_{20}H_{21}ClFNO_3$: C, 63.58; H, 5.60; N, 3.71. Found: C, 63.63; H, 5.41; N, 3.81.

tert-butyl 2-methyl-4-(2-fluoro-3-chlorophenyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta [b]pyridine-3-carboxylate (Compound 13): Crystallized from ethyl acetate/n-hexane. Yield: 49%. mp: 207 ºC. IR (ν, cm^{-1}): 3266 (N-H), 1696 (C=O, ester), 1631 (C=O, ketone). ^{1}H-NMR (δ, DMSO-d_6): 1.16 (9H; s; $COOC(C\underline{H}_3)_3$), 2.12-2.52 (4H; m; H-6, H-7), 2.24 (3H; s; 2-CH_3), 4.88 (H; s; 4-H), 7.07-7.32 (3H; m; Ar-H), 9.63 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6):

18.9, 24.1, 24.3, 24.5, 28.0, 32.0, 33.7, 79.4, 104.4, 115.0, 119.5, 125.4, 128.3, 129.7, 136.4, 146.2, 153.3, 155.8, 166.2, 165.9, 200.7. MS (m/z): 377 $[M]^+$. Anal. Calcd. for $C_{20}H_{21}ClFNO_3$: C, 63.58; H, 5.60; N, 3.71. Found: C, 63.27; H, 5.22; N, 3.84.

Benzyl 2-methyl-4-(2-fluoro-3-chlorophenyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (Compound 14): Crystallized from ethyl acetate. Yield: 48%. mp: 172 ºC. IR (ν, cm^{-1}): 3261 (N-H), 1699 (C=O, ester), 1633 (C=O, ketone). ^{1}H-NMR (δ, DMSO-d_6): 2.19-2.56 (4H; m; H-6, H-7), 2.32 (3H; s; 2-CH_3), 4.89, 4.99 (1H, AB system, J_{AB}=13.2 Hz, COOC$\underline{H}_2C_6H_5$), 4.95 (1H; s; H-4), 7.00-7.36 (8H; m; Ar-H), 9.88 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 19.3, 24.2, 31.9, 33.8, 65.3, 102.4, 115.5, 119.8, 125.4, 127.9, 128.1, 128.5, 128.6, 129.6, 135.9, 136.1, 136.8, 148.1, 153.5, 155.9, 164.7, 166.6, 200.1. MS (m/z): 411 $[M]^+$. Anal. Calcd. for $C_{23}H_{19}ClFNO_3$: C, 67.07; H, 4.65; N, 3.40. Found: C, 66.67; H, 4.67; N, 3.40.

Methyl 2-methyl-4-(2,3-dichlorophenyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (Compound 15): Crystallized from ethyl acetate/n-hexane. Yield: 62%. mp: 216 ºC. IR (ν, cm^{-1}): 3294 (N-H), 1741 (C=O, ester), 1640 (C=O gerilim, ketone). ^{1}H-NMR (δ, DMSO-d_6): 2.10-2.57 (4H; m; H-6, H-7), 2.29 (3H; s; 2-CH_3), 3.41 (3H; s; $COOCH_3$), 5.17 (1H; s; H-4), 7.14-7.37 (3H; m; Ar-H), 9.76 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 19.0, 23.7, 33.2, 36.4, 51.0, 103.1, 115.6, 127.8, 128.3, 129.8, 130.5, 131.2, 146.5, 147.0, 164.0, 166.8, 200.4. DEPT-135 (δ, DMSO-d_6): 19.0 (CH_3), 23.7 (CH_2), 33.2 (CH_2), 36.4 (CH), 51.0 (CH_3), 128.3 (CH), 129.8 (CH), 130.5 (CH). MS (m/z): 351 $[M-1]^+$. Anal. Calcd. for $C_{17}H_{15}Cl_2NO_3$: C, 57.97; H, 4.29; N, 3.98. Found: C, 57.91; H, 4.24; N, 3.90.

Ethyl 2-methyl-4-(2,3-dichlorophenyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (Compound 16): Crystallized from ethyl acetate. Yield: 56%. mp: 206 ºC. IR (ν, cm^{-1}): 3380 (N-H), 1675 (C=O, ester), 1639 (C=O, ketone). ^{1}H-NMR (δ, DMSO-d_6): 0.93 (3H; t; $COOCH_2C\underline{H}_3$), 2.14-2.56 (4H; m; H-6, H-7), 2.29 (3H; s; 2-CH_3), 3.85 (2H; q; $COO\underline{CH}_2CH_3$), 5.71 (1H; s; H-4), 7.15-7.38 (3H; m; Ar-H), 9.80 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 14.2, 19.1, 24.2, 33.7, 36.5, 59.4, 103.8, 116.0, 128.3, 128.8, 129.8, 130.7, 131.7, 147.0, 147.6, 164.4, 166.8, 200.8. MS (m/z): 366 $[M]^+$. Anal. Calcd. for $C_{18}H_{17}Cl_2NO_3$: C, 59.03; H, 4.68; N, 3.82. Found: C, 59.87; H, 4.56; N, 3.74.

2-Methoxyethyl 2-methyl-4-(2,3-dichlorophenyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (Compound 17): Crystallized from benzene/petroleum ether. Yield: 58%. mp: 153 ºC. IR (ν, cm^{-1}): 3263 (N-H), 1676 (C=O ester), 1637 (C=O, ketone). ^{1}H-NMR (δ, DMSO-d_6): 2.12-2.56 (4H; m; H-6, H-7), 2.30 (3H, s, 2-CH_3), 3.12 (3H; s; OCH3), 3.26-3.34 (2H; m; C$\underline{H}_2$OCH$_3$), 3.89-3.98 (2H; m; C$\underline{H}_2$CH$_2$OCH$_3$), 5.16 (H; s; 4-H), 7.15-7.37 (3H; m; Ar-H), 9.90 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 18.7, 23.7, 33.3, 36.0, 57.8, 62.2, 69.5, 102.9, 115.5, 127.7, 127.9, 128.2, 129.4, 130.1, 131.3, 146.8, 147.0, 166.3, 200.3. MS (m/z): 396 $[M]^+$. Anal. Calcd. for $C_{19}H_{19}Cl_2NO_4$: C, 57.59; H, 4.83; N, 3.53. Found: C, 57.70; H, 4.68; N, 3.43.

Allyl 2-methyl-4-(2,3-dichlorophenyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (Compound 18): Crystallized from ethyl acetate/n-hexane. Yield: 44%. mp: 192 ºC. IR (ν, cm^{-1}): 3315 (N-H), 1711 (C=O, ester), 1640 (C=O, ketone). ^{1}H-NMR (δ, DMSO-d_6): 2.10-2.55 (4H; m; H-6, H-7), 2.29 (3H; s; 2-CH_3), 4.32 (H; dd; C$\underline{H}_{2A}$-CH=CH$_2$), 4.39 (H; dd; C$\underline{H}_{2B}$-CH=CH$_2$), 4.89 (H; dd; CH$_2$CH=C$\underline{H}_{2A}$), 4.98 (H; dd; CH$_2$CH=C$\underline{H}_{2B}$), 5.17 (H; s; 4-H), 5.60-5.69 (H; m; C$\underline{H}$=CH$_2$), 7.14-7.35 (3H; m; Ar-H), 9.78 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 18.5, 23.7, 33.2, 36.7, 79.1, 104.8, 114.7, 127.6, 127.8, 128.2, 129.4, 130.3, 131.3, 132.1, 145.0, 146.6, 164.1, 165.9, 200.2. MS (m/z): 377 $[M-1]^+$. Anal. Calcd. for $C_{19}H_{17}Cl_2NO_3$: C, 60.33; H, 4.53; N, 3.70. Found: C, 60.13; H, 4.38; N, 3.83.

Isobutyl 2-methyl-4-(2,3-dichlorophenyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (Compound 19): Crystallized from ethyl acetate. Yield: 63%. mp: 234 ºC. IR (ν, cm^{-1}): 3306 (N-H), 1699 (C=O, ester), 1638 (C=O, ketone). ^{1}H-NMR (δ, DMSO-d_6): 0.58 (3H; d; COOCH$_2$CHC$\underline{H}_3$), 0.69 (3H; d; COO CH$_2$CHC$\underline{H}_3$), 1.68-1.76 (H; m; C$\underline{H}$(CH$_3$)$_2$), 2.14-2.55 (4H; m; H-6, H-7), 2.32 (3H; s; 2-CH_3), 3.58 (H; dd; C$\underline{H}_{2A}$CH(CH$_3$)$_2$), 3.70 (H; dd; C$\underline{H}_{2B}$CH(CH$_3$)$_2$), 5.17 (H; s; 4-H), 7.16-7.37 (3H; m; Ar-H), 9.78 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 18.6, 18.8, 20.7, 23.7, 27.0, 33.3, 35.9, 69.3, 103.1, 115.7, 127.8, 127.9, 129.1, 130.1, 131.4, 147.0, 147.1, 163.9, 166.4, 200.3. MS (m/z): 393 $[M-1]^+$. Anal. Calcd. for $C_{20}H_{21}Cl_2NO_3$: C, 60.92; H, 5.37; N, 3.55. Found: C, 60.94; H, 5.07; N, 3.69.

Tert-butyl 2-methyl-4-(2,3-dichlorophenyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (Compound 20): Crystallized from ethyl acetate/n-hexane. Yield: 54%. mp: 193 ºC. IR (ν, cm^{-1}): 3276 (N-H), 1697 (C=O, ester), 1634 (C=O,

ketone). ^{1}H-NMR (δ, DMSO-d_6): 1.14 (9H; s; COOC(C<u>H</u>$_3$)$_3$), 2.11-2.51 (4H; m; H-6, H-7), 2.21 (3H; s; 2-CH$_3$), 5.08 (H; s; 4-H), 7.14-7.39 (3H; m; Ar-H), 9.66 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 18.7, 23.5, 23.6, 23.7, 33.3, 35.9, 38.8, 63.7, 103.2, 115.6, 127.8, 127.9, 129.3, 130.2, 131.3, 132.7, 147.0, 163.9, 165.9, 200.4. MS (m/z): 394 $[M]^+$. Anal. Calcd. for $C_{20}H_{21}Cl_2NO_3$: C, 60.92; H, 5.37; N, 3.55. Found: C, 60.84; H, 5.47; N, 3.59.

Benzyl 2-methyl-4-(2,3-dichlorophenyl)-5-oxo-4,5,6,7-tetrahydro-1H-cyclopenta[b]pyridine-3-carboxylate (Compound 21): Crystallized from benzene/petroleum ether. Yield: 58%. mp: 129 ºC. IR (ν, cm^{-1}): 3257 (N-H), 1698 (C=O, ester), 1632 (C=O, ketone). ^{1}H-NMR (δ, DMSO-d_6): 2.11-2.56 (4H; m; H-6, H-7), 2.30 (3H; s; 2-CH$_3$), 4.87, 4.99 (1H, AB system, J_{AB}=12.8 Hz, COOC<u>H</u>$_2$C$_6$H$_5$), 5.20 (1H; s; H-4), 6.96-7.35 (8H; m; Ar-H), 9.79 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 19.3, 24.2, 33.7, 36.4, 65.1, 103.3, 116.2, 127.9, 128.0, 128.2, 128.4, 128.5, 128.7, 129.8, 130.7, 131.9, 132.8, 136.9, 147.4, 147.9. 165.4, 166.6, 200.8. MS (m/z): 427 $[M-1]^+$. Anal. Calcd. for $C_{23}H_{19}Cl_2NO_3$: C, 64.50; H, 4.47; N, 3.27. Found: C, 64.96; H, 4.27; N, 3.24.

Methyl 5-methyl-7-(2,3-difluorophenyl)-2,3,4,7-tetrahydrothieno[3,2-b]pyridine-6-carboxylate-1,1-dioxide (Compound 22): Yield: 61%. mp: 264 ºC. IR (ν, cm^{-1}): 3337 (N-H), 1683 (C=O), 1303, 1166 (S=O). ^{1}H-NMR (δ, DMSO-d_6): 2.28 (3H; s; 5-CH$_3$), 2.78 (H; ddd; H-3$_A$), 2.85 (H; ddd; H-3$_B$), 3.26 (H; ddd; H-2$_A$), 3.31 (H; ddd; H-2$_B$), 3.44 (3H; s; COOCH$_3$), 5.14 (1H; s; H-7), 6.69-7.22 (3H; m; Ar-H), 9.50 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 19.2, 23.2, 30.2, 49.2, 51.3, 99.7, 112.0, 115.7, 124.9, 125.4, 135.8, 142.7, 145.9, 148.3, 151.1, 167.0. MS (m/z): 354 $[M-1]^+$. Anal. Calcd. for $C_{16}H_{15}F_2NO_4S$: C, 54.08; H, 4.25; N, 3.94; S, 9.02. Found: C, 53.89; H, 4.26; N, 4.43; S, 9.18.

Ethyl 5-methyl-7-(2,3-difluorophenyl)-2,3,4,7-tetrahydrothieno[3,2-b]pyridine-6-carboxylate-1,1-dioxide (Compound 23): Yield: 75%. mp: 273 ºC. IR (ν, cm^{-1}): 3333 (N-H), 1686 (C=O), 1252, 1135 (S=O). ^{1}H-NMR (δ, DMSO-d_6): 0.99 (3H; t; COOCH$_2$C<u>H</u>$_3$), 2.28 (3H; s; 5-CH$_3$), 2.77 (H; ddd; H-3$_A$), 2.84 (H; ddd; H-3$_B$), 3.26 (H; ddd; H-2$_A$), 3.32 (H; ddd; H-2$_B$), 3.85 (H; dq; COOC<u>H</u>$_{2A}$-CH$_3$), 3.92 (H; dq; COOC<u>H</u>$_{2B}$-CH$_3$) 5.15 (H; s; H-7), 6.97-7.22 (3H; m; Ar-H), 9.48 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 14.2, 19.1, 23.2, 30.1, 49.1, 59.6, 99.9, 112.0, 115.6, 115.8, 125.0, 125.5, 135.9, 136.1, 142.6, 148.2, 166.4. MS (m/z): 368 $[M-1]^+$. Anal. Calcd. for $C_{17}H_{17}F_2NO_4S$: C, 55.28; H, 4.64; N, 3.79; S, 8.68. Found: C, 54.96; H, 4.26; N, 3.94; S, 8.65.

2-Methoxyethyl 5-methyl-7-(2,3-difluorophenyl)-2,3,4,7-tetrahydrothieno[3,2-b]pyridine-6-carboxylate-1,1-dioxide (Compound 24): Yield: 57. mp: 239 ºC'dir. IR (ν, cm^{-1}): 3343 (N-H), 1665 (C=O), 1279, 1096 (S=O). ^{1}H-NMR (δ, DMSO-d_6): 2.11 (H; ddd; H-3_A), 2.28 (3H; s; 5-CH_3), 2.43 (H; ddd; H-3_B), 3.02 (3H; s; OCH3), 3.08 (H; ddd; H-2_A), 3.21-3.35 (2H; m; C$\underline{H}_2$OCH$_3$), 3.39 (H; ddd; H-2_B), 3.78 (H; ddd; C$\underline{H}_{2A}$CH$_2$OCH$_3$), 3.93 (H; ddd; C$\underline{H}_{2B}$CH$_2$OCH$_3$), 4.59 (H; s; 7-H), 5.89 (H; s; N-H), 6.96-7.44 (3H; m; Ar-H). ^{13}C-NMR (δ, DMSO-d_6): 20.2, 33.8, 34.2, 48.6, 57.8, 65.9, 70.0, 82.5, 99.3, 111.7, 115.9, 123.8, 126.8, 133.0, 142.1, 148.4, 153.6, 166.4. MS (m/z): 398 $[M-1]^+$. Anal. Calcd. for $C_{18}H_{19}F_2NO_5S$: C, 54.13; H, 4.79; N, 3.51; S, 8.03. Found: C, 54.40; H, 4.55; N, 3.55; S, 7.89.

Allyl 5-methyl-7-(2,3-difluorophenyl)-2,3,4,7-tetrahydrothieno[3,2-b]pyridine-6-carboxylate-1,1-dioxide (Compound 25): Yield: 64%. mp: 240 ºC. IR (ν, cm^{-1}): 3339 (N-H), 1666 (C=O), gerilim), 1288, 1132 (S=O). ^{1}H-NMR (δ, DMSO-d_6): 2.12 (H; ddd; H-3_A), 2.29 (3H; s; 5-CH_3), 2.40 (H; ddd; H-3_B), 3.08 (H; ddd; H-2_A), 3.40 (H; ddd; H-2_B), 4.37 (H; dd; C$\underline{H}_{2A}$CH=CH$_2$), 4.42 (H; dd; C$\underline{H}_{2B}$CH=CH$_2$), 4.94 (H; dd; CH$_2$CH=C$\underline{H}_{2A}$), 5.02 (H; dd; CH$_2$CH=C$\underline{H}_{2B}$), 5.18 (H; s; 7-H), 5.66-5.73 (H; m; C$\underline{H}$=CH$_2$), 6.69-7.49 (3H; m; Ar-H), 9.53 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 20.8, 30.1, 34.3, 49.2, 64.3, 83.0, 99.8, 115.7, 117.3, 124.2, 125.4, 127.3, 129.6, 135.8, 142.5, 148.6, 150.2, 166.0. MS (m/z): 381 $[M]^+$. Anal. Calcd. for $C_{18}H_{17}F_2NO_4S$: C, 56.69; H, 4.49; N, 3.67; S, 8.41. Found: C, 57.08; H, 4.45; N, 3.72; S, 8.45.

Isobutyl 5-methyl-7-(2,3-difluorophenyl)-2,3,4,7-tetrahydrothieno[3,2-b]pyridine-6-carboxylate-1,1-dioxide (Compound 26): Yield: 68%. mp: 264 ºC. IR (ν, cm^{-1}): 3364 (N-H), 1683 (C=O), 1245, 1084 (S=O). ^{1}H-NMR (δ, DMSO-d_6): 0.55 (3H; d; COOCHC$\underline{H}_3$), 0.58 (3H; d; COOCHC$\underline{H}_3$), 1.48-1.57 (H; m; C$\underline{H}$(CH$_3$)$_2$), 2.13 (H; ddd; H-3_A), 2.32 (3H; s; 5-CH_3), 2.46 (H; ddd; H-3_B), 3.03 (H; ddd; H-2_A), 3.37 (H; ddd; H-2_B), 3.49 (H; dd; C$\underline{H}_{2A}$CH(CH$_3$)$_2$), 3.65 (H; dd; C$\underline{H}_{2B}$CH(CH$_3$)$_2$), 4.62 (H; s; 7-H), 5.88 (H; s; N-H), 7.01-7.45 (3H; m; Ar-H). ^{13}C-NMR (δ, DMSO-d_6): 18.9, 19.0, 20.7, 27.6, 34.3, 34.7, 49.2, 69.9, 83.0, 99.9, 115.7, 124.0, 125.2, 127.3, 133.6, 142.5, 148.8, 154.1, 166.8. MS (m/z): 397 $[M]^+$. Anal. Calcd. for $C_{19}H_{21}F_2NO_4S$: C, 57.42; H, 5.33; N, 3.52; S, 8.07. Found: C, 57.06; H, 4.94; N, 3.57; S, 8.34.

Tert-butyl 5-methyl-7-(2,3-difluorophenyl)-2,3,4,7-tetrahydrothieno[3,2-b]pyridine-6-carboxylate-1,1-dioxide (Compound 27): Yield: 58%. mp: 259 ºC. IR (ν, cm^{-1}): 3368 (N-

H), 1684 (C=O), 1304, 1133 (S=O). ^{1}H-NMR (δ, DMSO-d_6): 1.09 (9H; s; COOC(C<u>H</u>$_3$)$_3$), 2.12 (H; ddd; H-3$_A$), 2.26 (3H; s; 5-CH$_3$), 2.44 (H; ddd; H-3$_B$), 3.06 (H; ddd; H-2$_A$), 3.39 (H; ddd; H-2$_B$), 4.53 (H; s; 7-H), 5.89 (H; s; N-H), 6.99-7.27 (3H; m; Ar-H). ^{13}C-NMR (δ, DMSO-d_6): 20.5, 28.2, 28.4, 28.7, 30.3, 34.5, 49.1, 80.9, 92.6, 101.2, 115.6, 124.9, 126.0, 134.3, 136.1, 142.4, 147.3, 153.0, 166.5. MS (m/z): 397 [M]$^+$. Anal. Calcd. for $C_{19}H_{21}F_2NO_4S$: C, 57.42; H, 5.33; N, 3.52; S, 8.07. Found: C, 57.16; H, 5.28; N, 3.77; S, 8.63.

Benzyl 5-methyl-7-(2,3-difluorophenyl)-2,3,4,7-tetrahydrothieno[3,2-b]pyridine-6-carboxylate-1,1-dioxide (Compound 28): Yield: 67%. mp: 237 ºC'dir. IR (ν, cm^{-1}): 3341 (N-H), aromatik), 1665 (C=O), 1288, 1131 (S=O). ^{1}H-NMR (δ, DMSO-d_6): 2.14 (H; ddd; H-3$_A$), 2.33 (3H; s; 5-CH$_3$), 2.46 (H; ddd; H-3$_B$), 3.05 (H; ddd; H-2$_A$), 3.39 (H; ddd; H-2$_B$), 4.65 (H; s; 7-H), 4.77, 4.98 (1H, AB system, J_{AB}=13.2 Hz, COOC<u>H</u>$_2$C$_6$H$_5$), 5.94 (H; s; N-H) 6.81-7.55 (8H; m; Ar-H). ^{13}C-NMR (δ, DMSO-d_6): 20.8, 28.6, 34.7, 51.0, 66.4, 81.2, 90.1, 115.3, 115.5, 124.1, 125.8, 127.2, 127.7, 128.4, 128.6, 133.5, 133.6, 137.4, 143.6, 149.9, 154.6, 166.6. MS (m/z): 430 [M-1]$^+$. Anal. Calcd. for $C_{22}H_{19}F_2NO_4S$: C, 61.24; H, 4.44; N, 3.25; S, 7.43. Found: C, 61.52; H, 4.56; N, 3.29; S, 7.31.

Methyl 5-methyl-7-(2-fluoro-3-chlorophenyl)-2,3,4,7-tetrahydrothieno[3,2-b]pyridine-6-carboxylate-1,1-dioxide (Compound 29): Yield: 59%. mp:245 ºC. IR (ν, cm^{-1}): 3346 (N-H), 1663 (C=O), 1303, 1128 (S=O). ^{1}H-NMR (δ, DMSO-d_6): 2.27 (3H; s; 5-CH$_3$), 2.78 (H; ddd; H-3$_A$), 2.85 (H; ddd; H-3$_B$), 3.25 (H; ddd; H-2$_A$), 3.33 (H; ddd; H-2$_B$), 3.43 (3H; s; COOCH$_3$), 5.13 (1H; s; H-7), 7.08-7.37 (3H; m; Ar-H), 9.51 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 19.2, 23.2, 30.9, 49.2, 51.3, 99.7, 112.0, 119.7, 125.6, 129.2, 134.9, 135.1, 142.7, 148.3, 156.0, 167.0. EI-MS (m/z): 370 [M-1]$^+$. Anal. Calcd. for $C_{16}H_{15}ClFNO_4S$: C, 51.69; H, 4.07; N, 3.77; S, 8.62. Found: C, 51.91; H, 3.74; N, 3.89; S, 8.45.

Ethyl 5-methyl-7-(2-fluoro-3-chlorophenyl)-2,3,4,7-tetrahydrothieno[3,2-b]pyridine-6-carboxylate-1,1-dioxide (Compound 30): Yield: 56%. mp: 239 ºC. IR (ν, cm^{-1}): 3348 (N-H), 1663 (C=O), 1287, 1127 (S=O). ^{1}H-NMR (δ, DMSO-d_6): 0.97 (3H; t; COOCH$_2$C<u>H</u>$_3$), 2.12 (H; ddd; H-3$_A$), 2.28 (3H; s; 5-CH$_3$), 2.45 (H; ddd; H-3$_B$), 3.03 (H; ddd; H-2$_A$), 3.37 (H; ddd; H-2$_B$), 3.74 (H; dq; COOC<u>H</u>$_{2A}$-CH$_3$), 3.87 (H; dq; COOC<u>H</u>$_{2B}$-CH$_3$) 5.12 (H; s; H-7), 7.04-7.43 (3H; m; Ar-H), 9.51 (H; s; N-H). ^{13}C-NMR (δ, DMSO-d_6): 14.1, 20.7, 30.6, 34.6, 51.0, 59.6, 81.1, 90.8, 112.0, 129.4, 133.1, 135.4, 142.6, 148.2, 154.0, 156.5, 166.9. EI-MS

(m/z): 385 $[M]^+$. Anal. Calcd. for $C_{17}H_{17}ClFNO_4S$: C, 52.92; H, 4.44; N, 3.63; S, 8.31. Found: C, 52.22; H, 4.61; N, 3.81; S, 8.42.

2-Methoxythyl 5-methyl-7-(2-fluoro-3-chlorophenyl)-2,3,4,7-tetrahydrothieno[3,2-b]pyridine-6-carboxylate-1,1-dioxide (Compound 31): Yield: 64%. mp: 189 ºC. IR (ν, cm^{-1}): 3332 (N-H), 1665 (C=O), 1284, 1125 (S=O gerilim). ^{1}H-NMR (δ, DMSO-d_6): 2.12 (H; ddd; H-3_A), 2.28 (3H; s; 5-CH_3), 2.42 (H; ddd; H-3_B), 3.01 (3H; s; OCH3), 3.08 (H; ddd; H-2_A), 3.21-3.27 (2H; m; C$\underline{H}_2$OCH$_3$), 3.38 (H; ddd; H-2_B), 3.78 (H; ddd; C$\underline{H}_{2A}$CH$_2$OCH$_3$), 3.93 (H; ddd; C$\underline{H}_{2B}$CH$_2$OCH$_3$), 4.57 (H; s; 7-H), 5.88 (H; s; N-H), 7.02-7.38 (3H; m; Ar-H). ^{13}C-NMR (δ, DMSO-d_6): 20.7, 29.0, 34.6, 51.2, 58.3, 66.3, 70.5, 81.1, 90.5, 119.5, 124.7, 128.6, 129.5, 129.8, 133.0, 150.3, 154.2,166.9. EI-MS (m/z): 415 $[M]^+$. Anal. Calcd. for $C_{18}H_{19}ClFNO_5S$: C, 51.99; H, 4.61; N, 3.37; S, 7.71. Found: C, 51.10; H, 4.54; N, 3.49; S, 7.89.

Allyl 5-methyl-7-(2-fluoro-3-chlorophenyl)-2,3,4,7-tetrahydrothieno[3,2-b]pyridine-6-carboxylate-1,1-dioxide (Compound 32): Yield: 58%. mp: 232ºC'dir. IR (ν, cm^{-1}): 3335 (N-H), 1699 (C=O), 1281, 1129 (S=O). ^{1}H-NMR (δ, DMSO-d_6): 2.13 (H; ddd; H-3_A), 2.34 (3H; s; 5-CH_3), 2.44 (H; ddd; H-3_B), 3.03 (H; ddd; H-2_A), 3.39 (H; ddd; H-2_B), 4.27 (H; dd; C$\underline{H}_{2A}$CH=CH$_2$), 4.35 (H; dd; C$\underline{H}_{2B}$CH=CH$_2$), 4.75 (H; s; 7-H), 4.84 (H; dd; CH$_2$CH=C$\underline{H}_{2A}$), 4.93 (H; dd; CH$_2$CH=C$\underline{H}_{2B}$) 5.57-5.65 (H; m; C$\underline{H}$=CH$_2$), 5.86 (H; s; N-H) 7.22-7.57 (3H; m; Ar-H). ^{13}C-NMR (δ, DMSO-d_6): 20.8, 30.6, 34.2, 51.0, 66.3, 83.0, 99.6, 119.6, 124.8, 125.6, 128.7, 129.3, 132.7, 133.8, 148.8, 150.3, 154.5, 166.5. EI-MS (m/z): 397 $[M]^+$. Anal. Calcd. for $C_{18}H_{17}ClFNO_4S$: C, 54.34; H, 4.31; N, 3.52; S, 8.06. Found: C, 54.03; H, 4.53; N, 3.71; S, 8.55.

Isobutyl 5-methyl-7-(2-fluoro-3-chlorophenyl)-2,3,4,7-tetrahydrothieno[3,2-b]pyridine-6-carboxylate-1,1-dioxide (Compound 33): Yield: 66%. mp: 243 ºC'dir. IR (ν, cm^{-1}): 3339 (N-H), 1683 (C=O), 1304, 1132 (S=O). ^{1}H-NMR (δ, DMSO-d_6): 0.52 (3H; d; COOCHC$\underline{H}_3$), 0.56 (3H; d; COOCHC$\underline{H}_3$), 1.48-1.55 (H; m; C$\underline{H}$(CH$_3$)$_2$), 2.11 (H; ddd; H-3_A), 2.31 (3H; s; 5-CH_3), 2.44 (H; ddd; H-3_B), 3.02 (H; ddd; H-2_A), 3.38 (H; ddd; H-2_B), 3.47 (H; dd; C$\underline{H}_{2A}$CH(CH$_3$)$_2$), 3.62 (H; dd; C$\underline{H}_{2B}$CH(CH$_3$)$_2$), 4.58 (H; s; 7-H), 5.86 (H; s; N-H), 7.05-7.44 (3H; m; Ar-H). ^{13}C-NMR (δ, DMSO-d_6): 18.9, 19.0, 20.7, 27.7, 34.2, 34.7, 49.2, 69.9, 83.0, 90.2, 112.2, 124.8, 125.7, 128.6, 129.5, 131.1, 142.5, 156.5, 166.8. MS (m/z): 413 $[M]^+$.

Anal. Calcd. for $C_{19}H_{21}ClFNO_4S$: C, 55.14; H, 5.11; N, 3.38; S, 7.75. Found: C, 55.38; H, 4.51; N, 3.57; S, 7.27.

Tert-butyl 5-methyl-7-(2-fluoro-3-chlorophenyl)-2,3,4,7-tetrahydrothieno[3,2-b]pyridine-6-carboxylate-1,1-dioxide (Compound 34): Yield: 70%. mp: 241 ºC'dir. IR (ν, cm^{-1}): 3340 (N-H), 1689 (C=O), 1304, 1132 (S=O). ^{1}H-NMR (δ, DMSO-d_6): 1.05 (9H; s; $COOC(C\underline{H}_3)_3$), 2.10 (H; ddd; H-3_A), 2.23 (3H; s; 5-CH_3), 2.42 (H; ddd; H-3_B), 3.06 (H; ddd; H-2_A), 3.38 (H; ddd; H-2_B), 4.49 (H; s; 7-H), 5.86 (H; s; N-H), 7.05-7.40 (3H; m; Ar-H). ^{13}C-NMR (δ, DMSO-d_6): 20.0, 27.5, 27.6, 27.7, 30.3, 34.0, 48.5, 80.4, 92.1, 99.1, 124.4, 125.2, 128.4, 129.2, 130.6, 133.3, 149.8, 156.0, 166.0. MS (m/z): 413 $[M]^+$. Anal. Calcd. for $C_{19}H_{21}ClFNO_4S$: C, 55.14; H, 5.11; N, 3.38; S, 7.75. Found: C, 55.17; H, 4.95; N, 3.61; S, 7.05.

Benzyl 5-methyl-7-(2-fluoro-3-chlorophenyl)-2,3,4,7-tetrahydrothieno[3,2-b]pyridine-6-carboxylate-1,1-dioxide (Compound 35): Yield: 72%. mp: 208ºC. IR (ν, cm^{-1}): 3348 (N-H), 1664 (C=O), 1303, 1130 (S=O). ^{1}H-NMR (δ, DMSO-d_6): 2.12 (H; ddd; H-3_A), 2.33 (3H; s; 5-CH_3), 2.43 (H; ddd; H-3_B), 3.04 (H; ddd; H-2_A), 3.38 (H; ddd; H-2_B), 4.61 (H; s; 7-H), 4.74, 4,94 (1H, AB system, J_{AB}=13.2 Hz, $COOC\underline{H}_2C_6H_5$), 5.90 (H; s; N-H), 6.77-7.54 (8H; m; Ar-H). ^{13}C-NMR (δ, DMSO-d_6): 20.8, 29.0, 34.7, 49.2, 66.8, 83.0, 89.9, 124.9, 125.6, 127.7, 128.1, 128.6, 129.1, 129.6, 131.1, 132.8, 133.0, 136.7, 137.4, 142.5, 156.5, 166.6. EI-MS (m/z): 447 $[M]^+$. Anal. Calcd. for $C_{22}H_{19}ClFNO_4S$: C, 58.99; H, 4.28; N, 3.13; S, 7.16. Found: C, 58.12; H, 4.43; N, 3.34; S, 7.73.

Methyl 5-methyl-7-(2,3-dichlorophenyl)-2,3,4,7-tetrahydrothieno[3,2-b]pyridine-6-carboxylate-1,1-dioxide (Compound 36): Yield: 48%. mp: 230 ºC. IR (ν, cm^{-1}): 3373 (N-H), 1660 (C=O), 1299, 1127 (S=O). ^{1}H-NMR (δ, DMSO-d_6): 2.11 (H, ddd, H-3_A), 2.32 (3H; s; 5-CH_3), 2.42 (H, ddd, H-3_B), 3.01 (H, ddd, H-2_A), 3.34 (3H; s; $COOCH_3$), 3.40 (H, ddd, H-2_B), 4.69 (1H; s; H-7), 5.82 (H; s; N-H), 7.18-7.46(3H; m; Ar-H). ^{13}C-NMR (δ, DMSO-d_6): 20.8, 34.2, 34.8, 50.7, 51.1, 81.5, 91.2, 127.7, 128.8, 129.4, 129.8, 130.5, 131.8, 143.2, 153.9, 167.6. DEPT-135 (δ, DMSO-d_6): 20.8 (CH_3), 34.2 (CH), 34.8 (CH_2), 50.7 (CH_2), 51.1 (CH_3), 127.7 (CH), 128.8 (CH),129.4 (CH). EI-MS (m/z): 388 $[M]^+$. Anal. Calcd. for $C_{16}H_{15}Cl_2NO_4S$: C, 49.50; H, 3.89; N, 3.61; S, 8.26. Found: C, 49.10; H, 4.15; N, 3.62; S, 8.01.

Ethyl 5-methyl-7-(2,3-dichlorophenyl)-2,3,4,7-tetrahydrothieno[3,2-b]pyridine-6-carboxylate-1,1-dioxide (Compound 37): Yield: 53%. mp: 228 ºC. IR (ν, cm^{-1}): 3369 (N-

H), 1660 (C=O), 1299, 1093 (S=O). ^{1}H-NMR (δ, DMSO-d_6): 0.81 (3H; t; $COOCH_2C\underline{H}_3$), 2.12 (H; ddd; H-3_A), 2.31 (3H; s; 5-CH_3), 2.44 (H; ddd; H-3_B), 3.03 (H; ddd; H-2_A), 3.36 (H; ddd; H-2_B), 3.71 (H; dq; $COOC\underline{H}_{2A}$-CH_3), 3.82 (H; dq; $COOC\underline{H}_{2B}$-CH_3) 4.72 (H; s; H-7), 5.86 (H; s; N-H), 7.22-7.47 (3H; m; Ar-H). ^{13}C-NMR (δ, DMSO-d_6): 14.3, 20.6, 30.5, 34.3, 51.1, 58.5, 81.3, 91.8, 127.6, 128.6, 129.5, 130.5, 131.6, 131.9, 143.7, 153.7, 167.0. EI-MS (m/z): 401 $[M-1]^+$. Anal. Calcd. for $C_{17}H_{17}Cl_2NO_4S$: C, 50.76; H, 4.26; N, 3.48; S, 7.97. Found: C, 50.98; H, 4.22; N, 3.53; S, 8.03.

2-Methoxythyl 5-methyl-7-(2,3-dichlorophenyl)-2,3,4,7-tetrahydrothieno[3,2-b]pyridine-6-carboxylate-1,1-dioxide (Compound 38): Yield: 41%. mp: 196 ºC. IR (ν, cm^{-1}): 3345 (N-H), 1663 (C=O), 1355, 1129 (S=O). ^{1}H-NMR (δ, DMSO-d_6): 2.12 (H, ddd, H-3_A), 2.32 (3H, s, 5-CH_3), 2.44 (H, ddd, H-3_B), 3.02 (3H; s; OCH3), 3.08 (H, ddd, H-2_A), 3.21-3.29 (2H; m; $C\underline{H}_2OCH_3$), 3.40 (H, ddd, H-2_B), 3.78 (H; ddd; $C\underline{H}_{2A}CH_2OCH_3$), 3.92 (H; ddd; $C\underline{H}_{2B}CH_2OCH_3$), 4.73 (H; s; 7-H), 5.86 (H; s; N-H), 7.20-7.48 (3H; m; Ar-H). ^{13}C-NMR (δ, DMSO-d_6): 20.6, 34.3, 34.7, 48.9, 58.3, 65.6, 70.5, 91.4, 100.1, 127.5, 128.6, 129.8, 130.5, 131.6, 139.3, 143.5, 154.1, 166.9. EI-MS (m/z): 432 $[M]^+$. Anal. Calcd. for $C_{18}H_{19}Cl_2NO_5S$: C, 50.01; H, 4.43; N, 3.24; S, 7.42. Found: C, 50.22; H, 4.50; N, 3.31; S, 7.92.

Allyl 5-methyl-7-(2,3-dichlorophenyl)-2,3,4,7-tetrahydrothieno[3,2-b]pyridine-6-carboxylate-1,1-dioxide (Compound 39): Yield: 47%. mp: 188 ºC. IR (ν, cm^{-1}): 3342 (N-H), 1664 (C=O), 1303, 1129 (S=O). ^{1}H-NMR (δ, DMSO-d_6): 2.13 (H; ddd; H-3_A), 2.34 (3H; s; 5-CH_3), 2.44 (H; ddd; H-3_B), 3.03 (H; ddd; H-2_A), 3.39 (H; ddd; H-2_B), 4.27 (H; dd; $C\underline{H}_{2A}CH=CH_2$), 4.35 (H; dd; $C\underline{H}_{2B}CH=CH_2$), 4.75 (H; s; 7-H), 4.84 (H; dd; $CH_2CH=C\underline{H}_{2A}$), 4.93 (H; dd; $CH_2CH=C\underline{H}_{2B}$) 5.57-5.65 (H; m; $C\underline{H}=CH_2$), 5.86 (H; s; N-H), 7.22-7.57 (3H; m; Ar-H). ^{13}C-NMR (δ, DMSO-d_6): 20.8, 30.5, 34.1, 51.0, 65.5, 91.0, 100.1, 115.7, 127.6, 128.8, 129.8, 130.5, 131.7, 133.7, 139.3, 150.4, 154.4, 166.5. EI-MS (m/z): 413 $[M-1]^+$. Anal. Calcd. for $C_{18}H_{17}Cl_2NO_4S$: C, 52.18; H, 4.14; N, 3.38; S, 7.74. Found: C, 52.29; H, 4.26; N, 3.43; S, 7.72.

Isobutyl 5-methyl-7-(2,3-dichlorophenyl)-2,3,4,7-tetrahydrothieno[3,2-b]pyridine-6-carboxylate-1,1-dioxide (Compound 40): Yield: 58%. mp: 244 ºC. IR (ν, cm^{-1}): 3345 (N-H), 1663 (C=O), 1302, 1128 (S=O). ^{1}H-NMR (δ, DMSO-d_6): 0.52 (3H; d; $COOCHC\underline{H}_3$), 0.56 (3H; d; $COOCHC\underline{H}_3$), 1.47-1.54 (H; m; $C\underline{H}(CH_3)_2$), 2.12 (H; ddd; H-3_A), 2.30 (3H; s; 5-CH_3), 2.44 (H; ddd; H-3_B), 3.04 (H; ddd; H-2_A), 3.39 (H; ddd; H-2_B), 3.48 (H; dd;

C$\underline{H}_{2A}$CH(CH_3)$_2$), 3.61 (H; dd; C$\underline{H}_{2B}$CH(CH_3)$_2$), 4.73 (H; s; 7-H), 5.84 (H; s; N-H), 7.22-7.47 (3H; m; Ar-H). ^{13}C-NMR (δ, DMSO-d_6): 18.9, 19.0, 20.6, 27.7, 34.1, 34.8, 51.1, 68.9, 81.3, 91.1, 127.6, 128.7, 129.5, 130.5, 131.8, 133.2, 143.5, 154.1, 166.9. EI-MS (m/z): 429 $[M-1]^+$. Anal. Calcd. for $C_{19}H_{21}Cl_2NO_4S$: C, 53.03; H, 4.92; N, 3.25; S, 7.45. Found: C, 53.19; H, 4.89; N, 3.35; S, 7.79.

Tert-butyl 5-methyl--(2,3-dichlorophenyl)-2,3,4,7-tetrahydrothieno[3,2-b]pyridine-6-carboxylate-1,1-dioxide (Compound 41): Yield: 58%. mp: 248 ºC. IR (ν, cm^{-1}): 3344 (N-H), 1689 (C=O), 1364, 1156 (S=O). ^{1}H-NMR (δ, DMSO-d_6): 1.06 (9H; s; COOC(C$\underline{H}_3$)$_3$), 2.11 (H; ddd; H-3_A), 2.28 (3H; s; 5-CH_3), 2.44 (H; ddd; H-3_B), 3.06 (H; ddd; H-2_A), 3.37 (H; ddd; H-2_B), 4.65 (H; s; 7-H), 5.75 (H; s; N-H), 7.19-7.47 (3H; m; Ar-H). ^{13}C-NMR (δ, DMSO-d_6): 19.8, 27.5, 27.6, 27.7, 30.0, 34.1, 48.5, 80.6, 92.9, 101.9, 121.1, 128.0, 129.1, 130.8, 131.2, 131.4, 143.8, 152.6,166.1. EI-MS (m/z): 429 $[M-1]^+$. Anal. Calcd. for $C_{19}H_{21}Cl_2NO_4S$: C, 53.03; H, 4.92; N, 3.25; S, 7.45. Found: C, 53.38; H, 4.74; N, 3.35; S, 7.79.

Benzyl 5-methyl-7-(2,3-dichlorophenyl)-2,3,4,7-tetrahydrothieno[3,2-b]pyridine-6-carboxylate-1,1-dioxide (Compound 42): Yield: 55%. mp: 214 ºC. IR (ν, cm^{-1}): 3359 (N-H), 1661 (C=O), 1300, 1178 (S=O). ^{1}H-NMR (δ, DMSO-d_6): 2.13 (H; ddd; H-3_A), 2.35 (3H; s; 5-CH_3), 2.44 (H; ddd; H-3_B), 3.04 (H,; ddd; H-2_A), 3.39 (H; ddd; H-2_B), 4.73, 4,94 (1H, AB system, J_{AB}=12.8 Hz, COOC$\underline{H}_2C_6H_5$), 4.75 (H; s; 7-H), 5.88 (H; s; N-H), 6.77-7.56 (8H; m; Ar-H). ^{13}C-NMR (δ, DMSO-d_6): 20.7, 34.1, 34.7, 51.1, 64.3, 81.3, 90.9, 127.0, 127.7, 128.4, 128.8, 129.5, 129.9, 130.6, 130.8, 131.2, 131.9, 132.3, 137.3, 143.4, 154.7, 166.6. EI-MS (m/z): 464 $[M]^+$. Anal. Calcd. for $C_{22}H_{19}Cl_2NO_4S$: C, 56.90; H, 4.12; N, 3.02; S, 6.90. Found: C, 56.06; H, 4.43; N, 3.10; S, 6.95.

3.2. Pharmacology

Relexant effects of the compounds and nicardipine on isolated rat ileum, on rat thoracic artery and half maximal effective concentration (EC_{50}) of the selected compounds are given in Table 1 and Table 2, respectively.

Table **1.** Relexant effects of the synthesized compounds and nicardipine (10^{-5} mol/L).

Compound	Inhibition % [a]	Inhibition % [b]	Compound	Inhibition % [a]	Inhibition % [b]
1	89.00 ± 13.05	4.18 ±1.53*	**22**	78.67 ± 23.14	3.08 ±1.74*
2	93.50 ± 8.67	3.77 ±0.99*	**23**	88.00 ± 15.60	2.80 ± 1.82*
3	47.00 ± 23.07 *	-	**24**	0	-
4	58.50 ±14.27*	3.42 ± 1.31*	**25**	80.12 ±9.55	7.68 ±2.38
5	48.83 ± 8.04 *	-	**26**	47.40 ± 16.00*	-
6	27.50 ±10.75*	-	**27**	45.60±14.66 *	-
7	99.17 ± 2.04	2.15 ± 1.42 *	**28**	65.83 ±15.68 *	4.96 ± 1.39*
8	77.00 ± 21.37	3.42 ± 0.97*	**29**	91.40 ± 12.88	0
9	53.00 ± 17.58 *	2.12±1.60 *	**30**	89.40 ± 11.22	0
10	47.80 ± 18.66 *	-	**31**	26.25 ± 19.92 *	-
11	100.00 ±0	1.83 ±1.13*	**32**	88.33 ± 16.26	3.82±2.11*
12	100.00 ±0	2.73 ±1.19*	**33**	39.83 ±11.90*	0
13	43.50 ± 11.90 *	-	**34**	52.20 ± 20.00*	3.30 ± 2.71*
14	61.60 ± 28.95*	3.08 ± 0.78*	**35**	40.60 ± 16.47*	-
15	96.83 ± 4.99	5.38 ±1.78	**36**	82.67 ± 15.98	0
16	84.33 ± 23.35	4.62 ±2.77*	**37**	75.83±21.70	1.55±0.9*
17	76.67 ±19.79	1.72± 0.90*	**38**	48.67 ± 11.53 *	0
18	67.40 ± 27.29 *	3.10 ± 1.25*	**39**	60.33± 19.17 *	4.88± 2.89
19	88.00 ± 14.35	5.02 ±1.36*	**40**	73.83± 16.20 *	0
20	54.50 ± 26.40*	2.60 ± 1.54*	**41**	37.83 ±15.54 *	0
21	66.50 ± 22.00*	2.98 ± .0.74*	**42**	37.60 ±10.79 *	3.21 ± 2.04*
Nicardipine	93.30 ± 7.42	9.13 ±3.83	**Nicardipine**	93.30 ± 7.42	9.13 ±3.83

[a] Studies on isolated rat ileum precontracted with barium chloride ($4x10^{-3}$ M)
[b] Studies on rat thoracic artery precontracted with potassium chloride (67mmol/L)
***** $p < 0.05$, compared with control responses (n=6)

Table **2.** EC_{50} values of the synthesized compounds and nicardipine on isolated rat ileum.

Compound	EC_{50}
1	$0.34\pm0.17\times10^{-7}$ *
2	$2.66\pm1.53\times10^{-7}$
7	$0.14\pm0.08\times10^{-7}$ *
11	$1.32\pm0.35\times10^{-7}$
12	$2.88\pm1.67\times10^{-7}$
15	$4.63\pm2.98\times10^{-7}$
16	$6.22\pm4.78\times10^{-7}$
19	$0.85\pm0.68\times10^{-7}$
23	0.55±0.33x10-7*
25	$8.12\pm1.94\times10^{-7}$
28	$7.66\pm4.46\times10^{-7}$
29	$4.25\pm2.72\times10^{-7}$
30	$2.17\pm1.46\times10^{-7}$
32	$0.90\pm0.60\times10^{-7}$
36	$4.00\pm1.27\times10^{-6}$
39	$4.27\pm1.85\times10^{-7}$
Nicardipine	$1.33\pm0.34\times10^{-7}$

***** $p< 0.05$, compared with control responses

4. Discussion

In this work a series of condensed 1,4-dihydropyridines were prepared via modified Hantzsch reaction. The structure of the compounds were elucidated by IR, ^{1}H-NMR, ^{13}C-NMR, DEPT, COSY**,** X-ray analysis and mass spectra and were confirmed by elemental analysis. Their calcium channel modulator activities were investigated on isolated rat ileum and thoracic aorta.

In IR spectra, characteristic N-H, C=O (ester), C=O (ketone) and S=O stretching bonds were observed. In ^{1}H-NMR, while the protons of the cyclohexanone ring were at 2.10-2.59 ppm as multiplet, each proton of tetrahydrothiophene ring was observed at 2.10-3.40 ppm seperately and as dublet of dublet of dublets (ddd). The methyl and methine protons on DHP ring were seen at 2.21-2.35 ppm and 4.69-5.71 ppm, respectively. The protons, which are on the aromatic rings, were seen at 6.69-7.57 ppm. N-H signals were observed at either 5.75-5.94 ppm or 9.48-9.90 ppm as singlets. In ^{13}C-NMR spectra of the compounds the number of the signals fitted exactly the number of carbon atoms. In COSY spectra of Compound **15**, it has been determined that there is an interaction between the methylene groups of the cyclopentanone ring. The mass spectra of the compounds were recorded via electron

ionization technique. Molecular ion peak (M^+) or M-1 peak due to the aromatisation of the DHP ring to the pyridine analogue were seen in the spectra of all compounds. Cleavage of the ester groups and phenyl rings from the parent molecule are the further most observed fragmentations.

The structures of the compounds were also confirmed by elemental analysis and the results were within ± 0.4% of theoretical values for all compounds.

The structure of the compound 14 was also confirmed by X-ray analysis [21]. It was founded that, 1,4-DHP ring has very shallow boat conformation, whereas the oxocyclopentene ring is planar and there is an intermolecular N-H·····O hydrogen bond between the amine group and the carbonyl O atom of the oxoyclopentene ring of a neighbouring molecule.

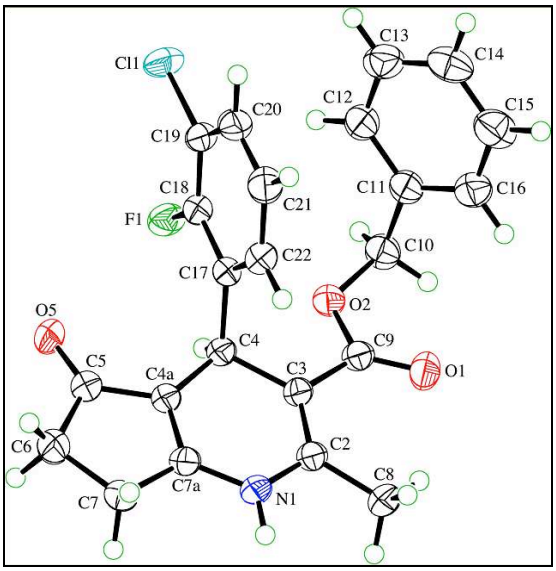


Figure 2: X-Ray diagram of compound **14**.

On isolated rat ileum strips precontracted with barium chloride ($4x10^{-3}$ M) compounds **2**, **7**, **11**, **12** and **15** are more active than the standard compound, nicardipine, at 10^{-5} M concentration. The most potent calcium antagonists are Compound **11** and **12** with 100 % inhibition. When the compounds are compared in respect to the fused rings, it has been observed that the compounds carrying cyclopentanone ring have higher activities than the derivatives bearing tetrahydrothiofen-1,1-dioxide ring. The compounds with methyl, ethyl and allyl esters increased the inhibition of the contraction more than the compounds having the other ester groups. Although there is not a distinct relationship between calcium modulator activity and the substitution of the phenyl ring, it has been determined that the most active compounds (**11** and **12**) bear 2-fluoro-3-chlorophenyl ring.

Half maximal effective concentration (EC_{50}) was also calculated for the compounds, which have possessed higher inhibition than 80 % on isolated rat ileum. The results indicated that most of the compounds, which have lower EC_{50} value than nicardipine, have again cyclopentanone ring.

Thirty two compounds, which possessed calcium antagonist activity more than 50 % on isolated rat ileum, were also investigated on rat thoracic artery precontracted with potassium chloride (67 mmol/L). It was determined that compound **1**, **15**, **16**, **19**, **25**, **28** and **39** are relatively active derivatives. The results indicate that 2,3-dichlorophenyl, 2,3-difluorophenyl rings; methyl, ethyl and allyl esters enhance the activity possitively. It was observed again that the compounds having cyclopentanone ring were more active.

When the obtained data are analysed, it can be observed that, most of the active compounds bear cyclopentanone ring fused to the 1,4-DHP ring and methyl, ethyl and allyl moieties in ester groups. While the compounds have high activities on isolated rat ileum, most of them show lower activities on rat thoracic aorta so it has to be emphasized that the synthesized compounds have spasmolytic activity rather than vasodilator activity.

Acknowledgements

This study was supported by Hacettepe University, Scientific Research and Development Office (Project No: 1713) and The Scientific and Technological Research Council of Turkey-National Scholarship Programme for PhD Students.

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